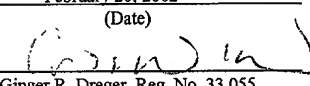


## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|           |   |  |   |  |
|-----------|---|--|---|--|
| Applicant | : | Wells et al.   | ) | Group Art Unit Unknown   |
|           |   |  | ) |  |
| Appl. No. | : | Unknown (This is a continuation<br>of copending Serial No.<br>10/043,833 filed January 11,<br>2002)                      | ) | I hereby certify that this correspondence and all<br>marked attachments are being deposited with the<br>United States Postal Service as first-class mail in<br>an envelope addressed to: United States Patent<br>and Trademark Office, P.O. Box 2327,<br>Arlington, VA 22202, on |
|           |   |  | ) |  |
| Filed     | : | Herewith   | ) | <u>February 20, 2002</u><br>(Date)   |
|           |   |  | ) |   |
| For       | : | METHODS FOR RAPIDLY<br>IDENTIFYING SMALL<br>ORGANIC MOLECULE<br>LIGANDS FOR BINDING TO<br>BIOLOGICAL TARGET<br>MOLECULES | ) | Ginger R. Dreger, Reg. No. 33,055  |
|           |   |  | ) |  |
| Examiner  | : | Unknown  |   |  |

PRELIMINARY AMENDMENT

United States Patent and Trademark Office  
P.O. Box 2327  
Arlington, VA 22202

Dear Sir:

The present Preliminary Amendment is filed concurrently with the filing of the above-identified continuation application. Please amend this application in the following aspects:

In the Specification:

Please insert the following sentence immediately following the title, as the first sentence of the specification:

- - This application is a continuation of copending application Serial No. 10/043,833 filed on January 11, 2002, which is a continuation of application Serial No. 09/981,547 filed on October 17, 2001, which is a division of application Serial No. 09/105,372 filed on June 26, 1998, now U.S. Patent No. 6,335,155 issued on January 1, 2002. - -

In the Claims:

**Appl. No.** : Unknown (This is a continuation of copending Serial No. 10/043,833 filed January 11, 2002)  
**Filed** : Herewith

Please cancel claim 1, without prejudice.

Please add the following new claims:

-- 40. (New) A method for identifying a ligand that binds to a target protein wherein said ligand is not a peptide and is less than about 2000 daltons in size, said method comprising:

- a) obtaining said target protein comprising a -SH group, masked -SH group, or activated -SH group;
- b) combining said target protein with one or more ligand candidates wherein said ligand candidates each comprises a disulfide bond, and wherein said ligand candidates are not peptides and are each less than about 2000 daltons in size;
- c) forming a target protein-ligand conjugate wherein at least one ligand candidate binds to the target protein and forms a disulfide bond with the target protein under disulfide exchange conditions; and
- d) detecting the formation of said target protein-ligand conjugate and identifying the ligand present in said conjugate.

41. (New) The method of claim 40 wherein the ligand is less than 1500 daltons.

42. (New) The method of claim 40 wherein the ligand is less than 1000 daltons.

43. (New) The method of claim 40 wherein the ligand is less than 750 daltons.

44. (New) The method of claim 40 wherein the ligand is less than 500 daltons.

45. (New) The method of claim 40 wherein step b) is performed in the presence of a reducing agent.

46. (New) The method of claim 40 wherein step c) is performed in the presence of a reducing agent.

**Appl. No.** : Unknown (This is a continuation of copending Serial No. 10/043,833 filed January 11, 2002)

**Filed** : Herewith

47. (New) The method of claim 45 or claim 46 wherein the reducing agent is 2-mercaptoethanol.

48. (New) The method of claim 40 wherein the formation of the target protein-ligand conjugate is detected using mass spectrometry.

49. (New) The method of claim 48 wherein the target protein-ligand conjugate is subjected directly to mass spectrometry analysis.

50. (New) The method of claim 48 wherein the target protein-ligand conjugate is fragmented prior to mass spectrometry analysis.

51. (New) The method of claim 49 or claim 50 wherein the mass spectrometry analysis also identifies the ligand in said conjugate.

52. (New) The method of claim 40 wherein the target protein-ligand conjugate is detected using NMR.

53. (New) The method of claim 52 wherein NMR also identifies the ligand in said conjugate.

54. (New) The method of claim 40 wherein the target protein-ligand conjugate is detected using X-ray crystallography.

55. (New) The method of claim 54 wherein X-ray crystallography also identifies the ligand in said conjugate.

56. (New) The method of claim 40 wherein the target protein-ligand conjugate is detected using capillary electrophoresis.

**Appl. No.** : Unknown (This is a continuation of copending Serial No. 10/043,833 filed January 11, 2002)  
**Filed** : Herewith

57. (New) The method of claim 40 wherein the target protein-ligand conjugate is detected using high performance liquid chromatography.

58. (New) The method of claim 40 wherein the target protein-ligand conjugate is detected using an assay based on the function of the target protein.

59. (New) A method for identifying a ligand that binds to a target protein wherein said ligand is not a peptide and is between about 200 and about 2000 daltons in size, said method comprising:

- a) obtaining said target protein comprising a -SH group, masked -SH group, or activated -SH group;
- b) combining said target protein with one or more ligand candidates in a mixture wherein said ligand candidates each comprises a disulfide bond, and wherein said ligand candidates are not peptides and are each less than about 2000 daltons in size;
- c) forming a target protein-ligand conjugate wherein at least one ligand candidate binds to the target protein and forms a disulfide bond with the target protein under disulfide exchange conditions;
- d) separating the target protein-ligand conjugate from the mixture; and
- e) identifying the ligand present in said conjugate.

60. (New) The method of claim 59 wherein the ligand is identified using mass spectrometry.

61. (New) The method of claim 59 wherein the ligand is identified by coupling the ligand to a probe.

62. (New) The method of claim 61 wherein the probe is a fluorescent marker.

63. (New) The method of claim 61 wherein the probe is a radioactive marker. - -

Appl. No. : Unknown (This is a continuation of copending Serial No. 10/043,833 filed January 11, 2002)

Filed : Herewith

Remarks

Claim 1 has been canceled, and claims 40-63 have been added by the foregoing amendments. The amended claims are fully supported by the specification as originally filed, and do not add new matter.

Please charge any additional fees, including any fees for United States Patent and extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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